Synthesis and Antibacterial Activity of U-100592 and U-100766, Two Oxazolidinone Antibacterial Agents for the Potential Treatment of Multidrug-Resistant Gram-Positive Bacterial Infections

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Bacterial resistance development has become a very serious clinical problem for many classes of antibiotics. The 3-aryl-2-oxazolidinones are a relatively new class of synthetic antibacterial agents, having a new mechanism of action which involves very early inhibition of bacterial protein synthesis. We have prepared two potent, synthetic oxazolidinones, U-100592 and U-100766, which are currently in clinical development for the treatment of serious multidrug-resistant Gram-positive bacterial infections caused by strains of staphylococci, streptococci, and enterococci. The *in vitro* and *in vivo* (po and iv) activities of U-100592 and U-100766 against representative strains are similar to those of vancomycin. U-100592 and U-100766 demonstrate potent *in vitro* activity against *Mycobacterium tuberculosis*. A novel and practical asymmetric synthesis of (5*S*)-(acetamidomethyl)-2-oxazolidinones has been developed and is employed for the synthesis of U-100592 and U-100766. This involves the reaction of *N*-lithioarylcarbamates with (*R*)-glycidyl butyrate, resulting in excellent yields and high enantiomeric purity of the intermediate (*R*)-5-(hydroxymethyl)-2-oxazolidinones.

Introduction

The increasing incidence of multidrug resistance among Gram-positive bacterial pathogens represents one of the major challenges in the 1990's for health care practitioners.[1-3] One particularly unsettling milestone has been the acquisition of resistance to vancomycin,[4] an antibiotic generally regarded as the agent of last resort for serious Gram-positive infections. Isolated reports from U.S. and U.K. hospitals have begun describing what is an alarming escalation in the percentage of vancomycin-resistant enterococcal (VRE) clinical isolates.[5,6] Since VRE strains also carry resistance to virtually all other known antibiotics,[7] the prognosis for patients with such refractory infections is grim; associated mortality rates above 35% have been reported.[8]

A problem of much larger dimension is the escalating incidence of the more virulent, methicillin-resistant *Staphylococcus aureus* (MRSA) among clinical isolates found throughout centers worldwide.[9] As with the VRE, many MRSA strains are resistant to most other antibiotics;[10,11] however, as yet, MRSA strains have remained susceptible to vancomycin. The sobering emergence of VRE pales in the face of projections from numerous infectious diseases experts,[12,13] who are of the opinion there is high likelihood *S. aureus* will, in time, also naturally acquire vancomycin resistance. Noble *et al.*[14] have observed transposon-mediated transmission of the vancomycin resistance genes to *S. aureus*, from a VRE (*Enterococcus faecalis*), in an experiment conducted on the skin of a mouse.

This growing problem of multidrug resistance has recently rekindled interest in the search for new antibiotic structural classes that inhibit or kill by novel mechanisms.[15] Clearly there is an urgent need for the discovery and development of new agents effective against the emerging and currently problematic Gram-positive pathogens MRSA, methicillin-resistant coagulase-negative staphylococci, VRE, and penicillin-resistant pneumococci,[16] as well as the perceived looming threat of a vancomycin-resistant *S. aureus*.

In a 1978 patent[17] issued to the EI DuPont de Nemours & Co., Inc., a series of 5-(halomethyl)-3-aryl-2-oxazolidinones were claimed to have activity against certain plant pathogens. Subsequent reports detailed a (5*R*)-(hydroxymethyl)-3-aryl-2-oxazolidinone, S-6123,[18] which demonstrated weak *in vitro* antibacterial activity against human pathogens.[19] Further optimization[20,21] led to the description in 1987 of two drug candidates, DuP 721 and DuP 105, members of a new class of parenterally and orally active, totally synthetic (5*S*)-(acetamidomethyl)-3-aryl-2-oxazolidinone antibacterial agents.[22]

The oxazolidinones have a novel mechanism of action that involves the inhibition of bacterial protein synthesis at a very early stage, prior to chain initiation.[23] DuP 721 demonstrated potent activity *vs* Gram-positive pathogens (including MRSA).[24] Gram-negative anaerobes, and *Mycobacterium tuberculosis*.[25] The *in vitro* development of bacterial resistance to either DuP 721 or DuP 105 could not be demonstrated.[26] While both DuP 721 and DuP 105 were entered into phase I clinical trials, the development of each was subsequently discontinued.[27] In drug safety studies conducted at The Upjohn Co.,[28] it was demonstrated that (±)-DuP 721 exhibited lethal toxicity in the rat, when dosed orally at 100 mg/kg b.i.d. for 30 days.

S-6123
DuP 721 R = MeCO
DuP 105 R = MeSO
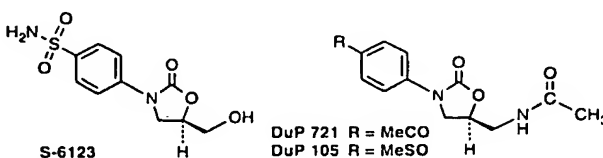
Realizing that oxazolidinones had promising potential to address the imminent critical need for new antibacterial agents, we instituted a program to improve upon the properties of DuP 721. Herein we describe U-100592 and U-100766, two novel oxazolidinones currently in clinical trials.

U-100592

U-100766
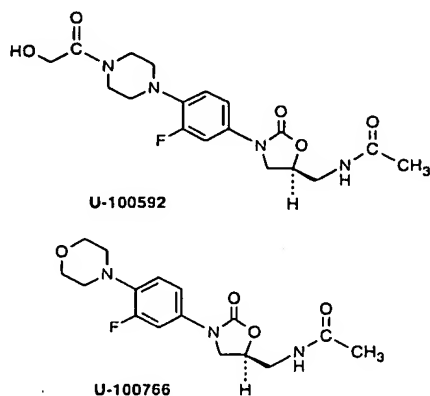
Results and Discussion

In prior disclosures, we have described (*S*)-3-(5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinones,[29] wherein one of the more potent analogues, U-97456, was substituted with a hydroxyacetyl moiety on the indoline nitrogen. E-3709[30] is an extremely active [4-(4'-pyridyl)-phenyl]oxazolidinone described by DuPont. We ultimately came to focus on exploring the (*S*)-3-(4-piperazinylphenyl)-5-(acetamidomethyl)-2-oxazolidinones,[31] based on considerations that the piperazine heterocycle would position the two nitrogens in similar loci to those found in both the 5'-indolinyl and the 4-(4'-pyridyl)-phenyl congeners. In the piperazinyl series, we again observed that an appendant hydroxyacetyl on the heterocyclic nitrogen afforded favorable antibacterial activity. Additional enhancements in *in vitro* and *in vivo* potency were attained by fluorine substitution at the phenyl 3-position, leading to U-100592.[32] A bioisostere of the piperazine, the morpholinyl analogue U-100766, contemporaneously emerged from our extensive structure–activity relationship (SAR) studies.

U-97456

E-3709
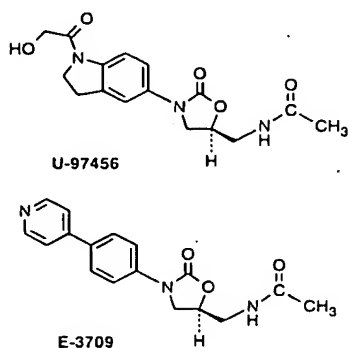
Only the oxazolidinone enantiomer with a (5*S*)-acetamidomethyl configuration possesses antibacterial activity.[33] We desired a more viable approach to the asymmetric synthesis of these oxazolidinones than that afforded by the Herweh–Kauffmann procedure,[34] which Wang *et al.*[35] had employed in a chiral fashion. This

method, employing a high-temperature isocyanate–epoxide cyclization, was deemed incompatible with our choices of phenyl substituents. There were also concerns regarding the hazards of phosgene use, which would be required for construction of noncommercially available isocyanates.
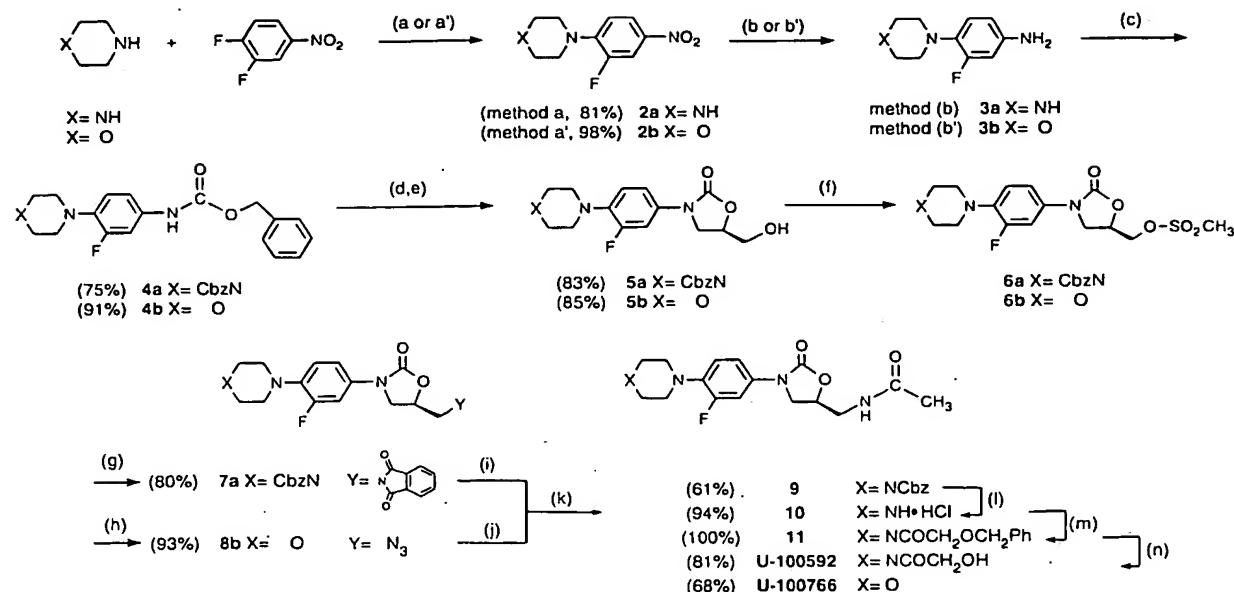
The syntheses of U-100592 and U-100766 share a common route, detailed in Scheme 1. Commencing with 3,4-difluoronitrobenzene, nucleophilic aromatic displacement, with excess piperazine (**1a**) or morpholine (**1b**), selectively gave the *p*-substituted nitrobenzene **2**. Reduction of **2a** or **2b** was followed by attachment of a carbobenzoxy (CBZ) *activating group* to the arylamines **3** (for **3a**, concomitant protection of the piperazine gave **4a**). Carbamate **4a** or **4b** was deprotonated with *n*-BuLi (THF, −78 °C), and then (*R*)-glycidyl butyrate [96–98% enantiomeric excess (ee); Lonza] was added and the mixture slowly allowed to warm to room temperature.[36] This sequence provided directly the (5*R*)-(hydroxymethyl)-2-oxazolidinone **5a** or **5b** in >80% yield, thus realizing a greater overall economy of chemical steps than the DuPont approach. As will be detailed elsewhere, crucial to the success of this new approach[37] was the selection of lithium as the base counterion.

With the alcohols **5** in hand, conversion to the (5*S*)-(acetamidomethyl)-2-oxazolidinones U-100592 and U-100766 was straightforward.[35] Activation as the mesylate **6** and then displacement with either potassium phthalimide to give **7** or with NaN₃ (on laboratory scale) to give **8b** was followed by formation of the intermediate 5-(aminomethyl)-2-oxazolidinones. This was accomplished by deblocking of the phthalimide **7a** with aqueous MeNH₂ or reduction of the azide **8b**. Treatment of the amines with Ac₂O and pyridine provided U-100766 (69% overall yield from **5b**, >99.8% ee[38]) and the CBZ-piperazine **9**. Catalytic hydrogenolysis of **9** provided the piperazine HCl salt **10**, which was acylated with (benzyloxy)acetyl chloride. Finally, benzylic hydrogenolytic cleavage of **11** gave U-100592 (37% overall yield from **5a**, >99.7% ee[38]).

U-100592 and U-100766 demonstrated excellent *in vitro* activity, at potency levels similar to that of vancomycin, against most staphylococci (including MRSA) and all streptococci and enterococci strains tested (selected strains, Table 1), without evidence of cross-resistance to any known antibiotic in the strains tested.[39] U-100766 was slightly less active than U-100592 *in vitro* against some organisms; neither drug demonstrated significant *in vitro* activity against Gram-negative aerobes. Both drugs had good anaerobe activity and demonstrated very potent *in vitro* activity against *M. tuberculosis*.[40]

U-100592 and U-100766 dosed orally (po) or subcutaneously (sq) were equipotent with vancomycin administered sq vs *S. aureus* UC 9213 in a lethal systemic mouse model (Table 2). Exceptional activity was also seen vs aminoglycoside-resistant *E. faecalis* and vancomycin-resistant *E. faecium* in lethal systemic mouse models.

Our new asymmetric synthesis of (5*S*)-(acetamidomethyl)-2-oxazolidinones involving the reaction of an *N*-lithioarylcarbamate with (*R*)-glycidyl butyrate (**1**) is applicable to the synthesis of widely divergent 3-(4-substituted-aryl)-2-oxazolidinones, (2) proceeds with high efficiency from commercially available reagents,

Scheme 1[a]

(method a, 81%) 2a X= NH
(method a', 98%) 2b X= O

method (b) 3a X= NH
method (b') 3b X= O

(75%) 4a X= CbzN
(91%) 4b X= O

(83%) 5a X= CbzN
(85%) 5b X= O

6a X= CbzN
6b X= O

(g) ⟶ (80%) 7a X= CbzN   Y= phthalimide   (i)
(h) ⟶ (93%) 8b X= O   Y= N₃   (j)   ⟶ (k)

(61%)	9	X= NCbz
(94%)	10	X= NH•HCl
(100%)	11	X= NCOCH₂OCH₂Ph
(81%)	U-100592	X= NCOCH₂OH
(68%)	U-100766	X= O

[a] (a) CH₃CN, reflux or (a') (i-Pr)₂EtN, EtOAc; (b) H₂, 5% Pd/C, THF or (b') HCO₂NH₄, 10% Pd/C, THF/MeOH; (c) CBZ-Cl, NaHCO₃ (or Na₂CO₃), acetone–H₂O; (d) n-BuLi, THF –78 °C; (e) (R)-glycidyl butyrate; (f) MsCl, Et₃N, CH₂Cl₂; (g) potassium phthalimide, CH₃CN, H₂O, reflux; (h) NaN₃, DMF, 75 °C; (i) aqueous MeNH₂, EtOH, reflux; (j) 10% Pd/C, H₂, EtOAc; (k) Ac₂O, pyr; (l) Pd/C, H₂, MeOH–CH₂Cl₂; (m) ClCOCH₂OCH₂Ph, Et₃N, CH₂Cl₂, 0 °C; (n) 10% Pd/C, H₂, MeOH–CH₂Cl₂.

Table 1. *In Vitro* Antibacterial Activity, Minimum Inhibitory Concentration (μg/mL)

organism	strain number	U-100592	U-100766	vancomycin
Staphylococcus aureus	UC[a] 9213	4	4	1
Staphylococcus aureus[c]	UC 12673	2	4	1
Staphylococcus aureus	ATCC[b] 29213	4	4	1
Staphylococcus epidermidis	UC 30031	1	1	1
Enterococcus faecalis	ATCC 29212	2	4	4
Enterococcus faecium	UC 12712	1	2	0.5
Streptococcus pneumoniae	UC 9912	0.5	1	0.5
Streptococcus pyogenes	UC 152	1	2	0.5
Escherichia coli	ATCC 25922	>64	>64	>64
Klebsiella pneumoniae	UC 12081	>64	>64	>64
Pseudomonas aeruginosa	ATCC 27853	>64	>64	>64
Bacteroides fragilis	ATCC 25285	1	1	>16[d]
Clostridium perfringens	ATCC 13124	1	1	1[e]
Mycobacterium tuberculosis	H37Rv	≤0.125	≤0.125	f

[a] Upjohn Culture (registered trademark of The Upjohn Co.). [b] American Type Culture Collection. [c] MRSA. [d] Comparative control value for clindamycin was 0.5 μg/mL. [e] Comparative control value for clindamycin was 0.06 μg/mL. [f] Comparative control value for isoniazid was 0.20 μg/mL.

Table 2. *In Vivo* Antibacterial Activity ED₅₀[a] (mg/kg)

organism	strain number	U-100592	U-100766	vancomycin[e]
Staphylococcus aureus[b]	UC 9213	1.9 (po)	5.6 (po)	3.9
Staphylococcus aureus[b]	UC 9213	0.9 (sq)	2.0 (sq)	3.9
Enterococcus faecalis[c]	UC 12379	1.3 (po)	10 (po)	<0.6
Enterococcus faecium[d]	UC 15090	12.5 (po)	24 (po)	>100

[a] Dose that protects 50% of the animals. [b] Organism demonstrates intermediate *in vivo* resistance to methicillin. [c] Gentamycin resistant. [d] Vancomycin resistant. [e] Control was dosed subcutaneously.

and (3) following side-chain manipulation, provides the targeted antibacterial oxazolidinones in extremely high ee. On the basis of their antibacterial potency, and acceptable pharmacokinetic[41] and drug safety profiles[42] in the rat and dog, U-100592 and U-100766 were selected for development as clinical candidates. These oxazolidinones are targeted as potential therapies for treating human infections caused by staphylococci, streptococci, and enterococci, including multidrug-resistant strains.

Experimental Section

Chemistry. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. ¹H NMR spectra were recorded on either a Bruker AM-300 or ARX-400 spectrometer. Chemical shifts are reported in δ units (ppm) relative to TMS as internal standard. Coupling constants (*J*) are reported in hertz (Hz). Electron impact (EI) mass spectra were obtained with an ionization voltage of 70 eV. Data are reported in the form *m/z* (rel intensity). All moisture-sensitive reactions were conducted under a nitrogen atmosphere in oven- or flame-dried glassware. Unless specified, all commercially available sol-

vents and reagents were used without further purification. THF was distilled under argon from sodium benzophenone ketyl prior to use. Solvent removal was accomplished by a rotary evaporator operating at house vacuum (40−50 Torr). Crude products were purified by medium pressure column chromatography over silica gel (EM Science; 230−400 mesh ASTM). Alternatively, smaller scale purifications were accomplished by preparative TLC (Analtech silica gel GF plates, 20 × 20 cm, 1000 μm). Silica gel (Analtech silica gel GF, 1 × 3 in., 250 μm thickness) plates were utilized for TLC analyses. Elemental analyses were within ±0.4% of the calculated values.

1-(2-Fluoro-4-nitrophenyl)piperazine, 2a. A solution of 12.0 g (75.42 mmol) of 3,4-difluoronitrobenzene in 150 mL of acetonitrile was treated with 16.24 g (188.6 mmol) of piperazine followed by warming at reflux for 3 h. The solution was cooled to ambient temperature and concentrated *in vacuo*. The resulting residue was diluted with 200 mL of water and extracted with ethyl acetate (3 × 250 mL). The combined organic layers were extracted with water (200 mL) and saturated sodium chloride solution (200 mL) followed by drying (Na$_2$SO$_4$). The solution was concentrated *in vacuo* to afford an orange oil which was chromatographed over 450 g of silica gel eluting initially with dichloromethane until the least polar fractions had eluted, and then elution was continued with 2% (v/v) methanol−dichloromethane and then with 10% (v/v) methanol−dichloromethane. These procedures afforded 13.83 g (81%) of **2a**, mp 68.5−71 °C. ^{1}H NMR (CDCl$_3$): δ 7.98 (dd, 1H, J = 2.6, 10.7 Hz), 7.91 (dd, 1H, J = 2.6, 13.1 Hz), 6.92 (t, 1H, J = 8.8 Hz), 3.27 (m, 4H), 3.05 (m, 4H). IR (mull): 2952, 2924, 2853, 1603, 1508, 1501, 1454, 1330, 1263, 1238, 1203, 881 cm^{-1}. MS: *m/z* 226 (5), 225 (34, M$^+$), 184 (12), 183 (100), 138 (4), 137 (22). Exact mass: calcd for C$_{10}$H$_{12}$FN$_3$O$_2$, 225.0913; found, 225.0906. Anal. (C$_{10}$H$_{12}$FN$_3$O$_2$) C, H, N.

***N*-Carbobenzoxy-3-fluoro-4-(*N*-carbobenzoxypiperazinyl)aniline, 4a.** A mixture of 145.4 g (0.646 mol) of **2a** and 14.0 g of 5% palladium on carbon in 1330 mL of tetrahydrofuran was shaken in a Paar shaker flask under 40 psi of H$_2$ for 1.5 h, while maintaining the reaction temperature below 50 °C. The reaction mixture was filtered through diatomaceous earth and the pad washed with 2 × 400 mL of tetrahydrofuran. The filtrate was concentrated, and the **3a** oil was azeotroped with 500 mL of acetone. The crude amine was immediately dissolved in 800 mL of acetone and added to a 5 L three-neck flask equipped with a mechanical stirrer, containing 1.6 L of 10% aqueous sodium carbonate. The mixture was cooled to 5 °C, and 200 mL (1.40 mol) of benzyl chloroformate was added dropwise over 20 min while maintaining the temperature between 7 and 10 °C. The mixture was then stirred for ·1 h at 5 °C and then allowed to stir overnight at room temperature. The mixture was filtered, and the solids were washed with tetrahydrofuran. The solid precipitate was collected by filtration, washed with 25% acetone−water, and then dried *in vacuo* at 45 °C, to give 352.7 g of off-white solid (93% pure by HPLC). A 10 g portion was purified by column chromatography on silica gel (10% methanol−methylene chloride) to give 8.1 g of **4a**. This was recrystallized from ethyl acetate−heptane to give 6.4 g of **4a** as a white solid, mp 154−155 °C. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.36 (m, 11H), 6.97 (d, J = 7.3 Hz, 1H), 6.87 (t, J = 8.9 Hz, 1H), 6.72 (s, 1H), 5.20 (s, 2H), 5.17 (s, 2H), 3.68 (t, J = 5.0 Hz, 4H), 3.00 (brs, 4H). IR (mineral oil mull, cm^{-1}): 3284, 1713, 1691, 1532, 1465, 1455, 1432, 1254. MS: *m/z* 463 (17, M$^+$), 355 (37), 329 (12), 328(15), 264 (31), 220 (7), 91 (100). Exact mass: calcd for C$_{26}$H$_{26}$FN$_3$O$_4$, 463.1907; found, 463.1914. Anal. (C$_{26}$H$_{26}$FN$_3$O$_4$) C, H, N.

(*R*)-[*N*-3-[3-Fluoro-4-[*N*-1-(4-carbobenzoxy)piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methanol, 5a. To a mixture of 4.857 g (10.49 mmol) of **4a** in 50 mL of freshly distilled tetrahydrofuran at −78 °C under nitrogen was added 6.8 mL (10.88 mmol) of 1.6 M *n*-butyllithium−hexane dropwise over 5 min. After 1.5 h, 1.55 mL of (*R*)-glycidyl butyrate was added and the mixture allowed to stir at −78 °C for 1 h and then at room temperature for 3.5 h (the mixture became thick with solid precipitation). Saturated aqueous ammonium chloride (25 mL) was added followed by 25 mL of ethyl acetate and 5

mL of water. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried (MgSO$_4$) and concentrated under reduced pressure to provide 5.655 g of **5a** as a white solid. The solid was triturated with ethyl acetate−hexane (1:1) in a warm water bath for 30 min and then refrigerated; the solids were collected by vacuum filtration to provide 3.753 g (83%) of **5a** as white solids, mp 156−157 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.45 (dd, J = 14.2 Hz, J = 2.6 Hz, 1H), 7.35 (m, 5H), 7.11 (dd, J = 7.7 Hz, J = 2.6 Hz, 1H), 6.92 (t, J = 9.1 Hz, 1H), 5.16 (s, 2H), 4.74 (m, 1H), 3.96 (m, 3H), 3.69 (m, 5H), 3.01 (s, br, 4H). IR (mineral oil mull, cm^{-1}): 3428, 1745, 1668, 1520, 1451, 1243. MS: *m/z* 429 (98.0, M$^+$), 430 (24.8), 294 (22.8), 265 (25.4), 91 (100), 56 (60.0). [α]^{20}$_D$ −32° (*c* 0.991, CHCl$_3$). Anal. (C$_{22}$H$_{24}$FN$_3$O$_5$) C, H, N.

(*R*)-*N*-[[3-[3-Fluoro-4-[*N*-1-(4-carbobenzoxy)piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]phthalimide, 7a. To a mixture of 13.936 g (32.48 mmol) of **5a** and 10.0 mL (71.88 mmol) of triethylamine in 350 mL of methylene chloride at 0 °C was added 3.0 mL (38.76 mmol) of methanesulfonyl chloride dropwise over 2 min. The mixture was stirred at 0 °C for 1.5 h and at room temperature for 3 h, the mixture was washed with 300 mL water, and the aqueous layer was extracted with methylene chloride (50 mL). Ethyl acetate (250 mL) was added to the combined organic layers; these were dried (MgSO$_4$) and concentrated under reduced pressure to give **6a** as a yellow foamy solid. This was taken up into 500 mL of acetonitrile and 2.5 mL of water and 18.193 g (98.22 mmol) of potassium phthalimide added. The mixture was heated to· reflux for *ca.* 48 h and then concentrated under reduced pressure to a yellow gum. The gum was triturated with 400 mL of ethyl acetate−hexane (1:1) followed by the addition of 200 mL of ethyl acetate. Upon concentration of the mixture under reduced pressure to 100 mL, a white precipitate formed, this was cooled to 4 °C, and the solids were collected to provide 8.338 g of **7a**. The filtrate was passed over a 34 cm × 5.5 cm silica gel column, eluting with 400 mL of 25% ethyl acetate−hexane and then with 1 L each of 50%, 75%, and 100% ethyl acetate−hexane. The appropriate fractions were combined to provide 6.121 g of **7a** as a light yellow solid; total recovery was 14.459 g (80%) of **7a**, mp 153−156 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.88 (m; 2H), 7.76 (m, 2H), 7.38 (m, 6H), 7.10 (dd, J = 8.8 Hz, J = 2.7 Hz, 1H), 6.92 (t, J = 9.1 Hz, 1H), 5.16 (s, 2 H), 4.97 (m, 1H), 4.13 (dd, J = 14.2 Hz, J = 6.6 Hz, 1H), ·4.08 (t, J = 8.8 Hz, 1H), 3.97 (dd, J = 14.1 Hz, J = 5.8 Hz, 1H), 3.86 (dd, J = 9.1 Hz,· J = 5.9 Hz, 1H), 3.68 (t, J = 4.8 Hz, 4H), 3.01 (s, br, 4H). IR (mineral oil mull, cm^{-1}): 1747, 1722, 1715, 1695. MS: *m/z* 558 (26.1, M$^+$), 382 (43.0), 91 (100), 56 (59.1), 43 (32.5). Anal. (C$_{30}$H$_{27}$FN$_4$O$_6$) C, H, N.

(*S*)-*N*-[[3-[3-Fluoro-4-[*N*-1-(4-carbobenzoxy)piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, 9. A mixture of 14.459 g (25.88 mmol) of **7a** and 30 mL of 40% methylamine in water (348.5 mmol) and 300 mL of ethanol was heated to reflux for 5.5 h; then additional methylamine solution (5 mL) was added. The mixture was heated to reflux for 1 h and then concentrated under reduced pressure. The residue was dissolved in 150 mL of pyridine, the mixture cooled to 0 °C, and acetic anhydride (50 mL) added. The mixture was allowed to stir at room temperature overnight and then concentrated by bulb-to-bulb distillation under reduced pressure. The crude was then taken up in 10% methanol−ethyl acetate and concentrated under reduced pressure to provide 15.92 g of crude **9** as a white solid. This was slurried in 150 mL of methylene chloride and filtered. The filtrate was placed upon a 11 cm × 13 cm, 70−230 μm silica gel column and eluted with a methanol−ethyl acetate gradient (0−5% MeOH); the appropriate fractions were combined to provide 7.42 g (61%) of **9** as a white solid, mp 174−176 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.44 (dd, J = 14.1 Hz, J = 2.6 Hz, 1H), 7.37 (m, 5H), 7.06 (d, J = 8.8 Hz, 1H), 6.90 (t, J = 9.1 Hz, 1H), 6.29 (t, br, J = *ca.* 11 Hz, 1H), 5.16 (s, 2H), 4.77 (m, 1H), 4.02 (t, J = 9.0 Hz, 1H), 3.75 (dd, J = 9.1 Hz, J = 6.9 Hz, 1H), 3.64 (m, 6H), 3.00 (s, br, 4H), 2.02 (s, 3H). IR (mineral oil mull, cm^{-1}): 3306, 1750, 1682, 1647, 1520. MS: *m/z* 470 (43.3, M$^+$), 426 (17.9), 91 (100), 56 (70.5). [α]^{20}$_D$ −19° (*c* 0.8121, DMSO). Anal. (C$_{24}$H$_{27}$FN$_4$O$_5$) C, H, N.

(S)-N-[[3-[3-Fluoro-4-(N-1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, Hydrochloride, 10. A mixture of 15.660 g (33.32 mmol) of 9 and 2.250 g of 10% palladium on carbon in 750 mL of methanol and 250 mL of methylene chloride was stirred under hydrogen (balloon) overnight. The mixture was then filtered through diatomaceous earth. The filter cake was washed with 200 mL of 25% methylene chloride in methanol followed by 100 mL of ethyl acetate, and the filtrates were concentrated to give 12.040 g of off-white solids. The solids were triturated with 200 mL of 10% methanol–ethyl acetate in a warm water bath for 30 min and then cooled to 0 °C. The solids were collected to provide 11.696 g (94%) of 10 as a white solid, mp 214–217 °C. ¹H NMR (CDCl₃ + MeOH-d₄, 300 MHz): δ 7.45 (dd, J = 14.2 Hz, J = 2.5 Hz, 1H), 7.07 (dd, J = 11.5 Hz, J = 9.6 Hz, 1H), 6.96 (t, J = 9.1 Hz, 1H), 4.77 (m, 1H), 4.04 (t, J = 9.1 Hz, 1H), 3.76 (dd, J = 9.2 Hz, J = 6.7 Hz, 1H), 3.65 (dd, J = 11.2 Hz, J = 3.4 Hz, 1H), 3.57 (dd, J = 14.6 Hz, J = 5.7 Hz, 1H), 3.20 (s, 8H), 2.01 (s, 3H). IR (mineral oil mull, cm⁻¹): 1742, 1656, 1517, 1237. MS: m/z 336 (62.4, M⁺), 294 (100), 250 (24.5), 56 (24.5), 29 (19.6). [α]²⁰_D −22° (c 0.948, DMSO).

(S)-N-[[3-[3-Fluoro-4-[N-1-[(4-benzyloxy)acetyl]piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, 11. To a suspension of 3.569 g (9.594 mmol) of 10 in 200 mL of methylene chloride at 0 °C were added 3.0 mL (21.52 mmol) of triethylamine and then 2.0 mL (12.67 mmol) of (benzyloxy)acetyl chloride, dropwise over 2 min. The mixture became homogeneous, was stirred at 0 °C for 2 h and then at room temperature for 2.5 h, and then washed with water (2 × 100 mL), and the combined aqueous layers were extracted with methylene chloride (50 mL). Ethyl acetate (50 mL) was added to the combined organic layers to provide a homogeneous mixture, which was dried (MgSO₄) and concentrated to provide 5.040 g (100%) of 11 as a white solid, mp 164–166 °C, which was used in the next step without further purification. ¹H NMR (CDCl₃, 300 MHz): δ 7.45 (dd, J = 14.1 Hz, J = 2.6 Hz, 1H), 7.34 (m, 5H), 7.07 (dd, J = 10.4 Hz, J = 8.8 Hz, 1H), 6.88 (t, J = 9.1 Hz, 1H), 6.31 (t, br, J = ca. 11 Hz, 1H), 4.76 (m, 1H), 4.62 (s, 2H), 4.23 (s, 2H), 4.01 (t, J = 9.0 Hz, 1H), 3.75 (m, 3H), 3.62 (m, 4H), 3.01 (s, 4H), 2.02 (s, 3H). IR (mineral oil mull, cm⁻¹): 1757; 1673, 1643, 1521, 1227. MS: m/z 484 (86.2, M⁺), 440 (30.1), 306 (66.1), 91 (100), 56 (72).

(S)-N-[[3-[3-Fluoro-4-[N-1-(4-hydroxyacetyl)piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, U-100592. A mixture of 29.04 g (60.0 mmol) of 11 and 8.114 g of 10% palladium on carbon in 2 L of 33% (v/v) methylene chloride–methanol was stirred under hydrogen (balloon) overnight, filtered over diatomaceous earth, and concentrated under reduced pressure to give a solid. This was purified by silica gel chromatography (49 cm × 5 cm column) and eluted with a methanol–methylene chloride gradient (1 L each, 3%, 5%, 7%, 9%, and 11% MeOH). The appropriate fractions were pooled to provide a foamy solid, which was triturated with 10% methanol–ethyl acetate to provide 19.239 g (81%) of U-100592 as a white solid, mp 175–176 °C. ¹H NMR (CDCl₃, 300 MHz): δ 7.47 (dd, J = 14.1 Hz, J = 2.6 Hz, 1H), 7.07 (d, J = ca. 9 Hz, 1H), 6.91 (t, J = 9.1 Hz, 1H), 6.21 (t, br, 1H), 4.78 (m, 1H), 4.21 (d, 4.4 Hz, 2H), 4.02 (t, J = 9.0 Hz, 2H), 3.84 (m, 2H), 3.74 (dd, J = 9.1 Hz, J = 6.7 Hz, 1H), 3.63 (m, 2H), 3.45 (m, 2H), 3.06 (t, J = 5.1 Hz, 4H), 2.02 (s, 3H). IR (mineral oil mull, cm⁻¹): 3453, 3295, 1730, 1647, 1520, 1239. MS: m/z 394 (65.6), 350 (88.3), 306 (72.4), 266 (42.6), 56 (100). Exact mass: calcd for C₁₈H₂₃FN₄O₅, 394.1652; found, 394.1651. [α]²⁰_D −21° (c 0.853, DMSO). Anal. (C₁₈H₂₃FN₄O₅) C, H,N.

3-Fluoro-4-morpholinylnitrobenzene, 2b. To a solution of 26.0 mL (297.2 mmol) of morpholine and 51.0 mL (293.0 mmol) of N,N-diisopropylethylamine in 150 mL of ethyl acetate was added slowly 30.0 mL (271.0 mmol) of 3,4-difluoronitrobenzene via an addition funnel. After the addition was ca. two-thirds complete, the reaction mixture had warmed to >35 °C. The flask was cooled in an ice bath, the remaining 3,4-difluoronitrobenzene added over the next 30 min, and mixture gradually warmed to room temperature overnight. Methylene chloride (100 mL), ethyl acetate (400 mL), and water (200 mL) were added to the reaction mixture, which contained a yellow precipitate. The phases were separated, and the aqueous

portion was extracted with ethyl acetate (3 × 100 mL). The combined organic portions were dried (Na₂SO₄) and concentrated to give 64.905 g of crude 2b as a yellow solid, which was recrystallized from acetone and water to give 60.096 g (98% yield) of 2b as a yellow solid, mp 111–112 °C. ¹H NMR (CDCl₃, 300 MHz): δ 7.99 (ddd, J = 9.0 Hz, J = 2.7 Hz, J′ = 1.2 Hz, 1H), 7.91 (dd, J = 13.2 Hz, J = 2.7 Hz, 1H), 6.92 (t, J = 9.0 Hz, 1H), 3.88 (m, 4H), 3.29 (m, 4H). ¹³C NMR (75.47 MHz, CDCl₃): 49.52, 49.59, 66.23, 112.21 (d, J = 26.11 Hz), 116.54 (d, J = 3.6 Hz), 120.64 (d, J = 2.6 Hz), 140.47 (d, J = 7.5 Hz), 145.13 (J = 7.7 Hz), 152.75 (d, J = 249.1 Hz). IR (mineral oil mull, cm⁻¹): 2925, 1604, 1517, 1496, 1330, 1245, 1124, 950. MS: m/z 226 (89.6, M⁺), 168 (100), 138 (23.5), 122 (13.2). Exact mass: calcd for C₁₀H₁₁FN₂O₃, 226.0754; found, 226.0747. Anal. (C₁₀H₁₁FN₂O₃) C, H, N.

3-Fluoro-4-morpholinylaniline, 3b. To a solution of 30.690 g (135.7 mmol) of 2b in 80 mL of tetrahydrofuran and 320 mL of methanol (320 mL) was added 34.064 g (540.2 mmol) of ammonium formate. The flask was alternately evacuated and filled with nitrogen (3×) and cooled to 0 °C; then 10% palladium on carbon was added (0.791 g), and the system was again evacuated and filled with nitrogen. After stirring for 2 h, the reaction mixture was filtered through a plug of diatomaceous earth, which was then washed with tetrahydrofuran (30 mL) and ethyl acetate (60 mL). The volume of the solution was reduced to 300 mL; then water (250 mL) and ethyl acetate (300 mL) were added and the phases separated, and the aqueous portion was extracted with ethyl acetate (1 × 200 mL, 2 × 100 mL). The combined organic portions were washed with saturated sodium chloride (150 mL), dried (MgSO₄), and evaporated to give 29.310 g of crude 3b as a yellow solid which was immediately taken on "as is" in the next reaction. ¹H NMR (CDCl₃, 300 MHz): δ 6.79 (m, 1H), 6.41 (overlapping m, 2H), 3.84 (m, 4H), 3.56 (br s, 2H), 2.96 (m, 4H). ¹³C NMR (75.47 MHz, CDCl₃): 51.70, 51.72, 67.01, 103.81 (d, J = 23.7 Hz), 110.71 (d, J = 2.5 Hz), 120.25 (d, J = 3.9 Hz), 131.30 (d, J = 9.43 Hz), 143.22 (d, J = 10.3 Hz), 156.69 (d, J = 245.0 Hz).

N-Carbobenzoxy-3-fluoro-4-morpholinylaniline, 4b. To a solution of 3b (29.310 g, crude, 135.7 mmol) in acetone (500 mL) and water (250 mL) at 0 °C were added 23.454 g (279.2 mmol) of sodium bicarbonate and then 20.0 mL (140.1 mmol) of benzyl chloroformate over 6 min via syringe. The mixture was stirred overnight and then poured onto 500 mL of ice and 1.2 L of water and the solid filtered and washed thoroughly with water (3 × 250 mL) to give 41.500 g (93%) of 4b as a cream-colored solid, which was recrystallized from acetone and water to give 31.343 g (70%) of 4b, as cream-colored crystals, mp 123–124 °C. Three additional crops of slightly less pure material (9.89 g, 21%) were also collected. ¹H NMR (CDCl₃, 300 MHz): δ 7.35 (m, 6H), 6.93 (m, 3H), 5.16 (s, 2H), 3.85 (t, J = 4.5 Hz, 4H), 3.01 (t, J = 4.5 Hz, 4H). IR (mineral oil mull, cm⁻¹): 3321, 2924, 1706, 1534, 1378, 1281, 1239, 1120. MS: m/z 330 (67.6, M⁺), 195 (98.1), 91 (100). Exact mass: calcd for C₁₈H₁₉FN₂O₃, 330.1380; found, 330.1373. Anal. (C₁₈H₁₉-FN₂O₃) C, H, N.

(R)-[N-3-(3-Fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methanol, 5b. To a solution of 40.604 g (123.0 mmol) of 4b in tetrahydrofuran (500 mL) under nitrogen at −78 °C was added n-butyllithium (77 mL, 1.6 M in hexane, 123.2 mmol) over 20 min via syringe. The solution was stirred at −78 °C for 35 min; then a tetrahydrofuran solution (25 mL) of (R)-glycidyl butyrate (17.8 mL, 125.7 mmol) was added in a dropwise fashion via addition funnel, over 30 min. After stirring at −78 °C for 1 h, the bath was removed and the reaction mixture was stirred at room temperature overnight. The reaction was then quenched with 20 mL of saturated ammonium chloride, ethyl acetate (300 mL), saturated ammonium chloride (400 mL), and water (300 mL) were added, the phases were separated, and the aqueous portion was extracted with ethyl acetate (3 × 300 mL). The combined organic portions were washed with saturated sodium chloride, dried (MgSO₄), and evaporated to give 5b (60.725 g) as a yellow solid; this was recrystallized from ethyl acetate and hexanes to give 30.814 g (85%) of 5b as a light gray amorphous solid, mp 112–114 °C. A second crop (2.431 g, 7%) of less pure

material was obtained. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.44 (dd, J = 14.4 Hz, J = 2.4 Hz, 1H), 7.10 (dd, J = 8.4 Hz, J = 1.6 Hz, 1H), 6.91 (t, J = 8.8 Hz, 1H), 4.73 (m, 8 lines, 1H), 3.96 (overlapping m, 3H), 3.86 (t, J = 4.8 Hz, 4H), 3.74 (m, 1H), 3.04 (t, J = 4.8 Hz, 4H), 2.93 (t, J = 6.4 Hz, 1H). IR (mineral oil mull, cm^{-1}): 3432, 3263, 2925, 1748, 1734, 1523, 1465, 1454, 1441, 1424, 1231. MS: *m/z* 296 (100, M$^+$), 238 (41.6), 151 (14.2). Exact mass: calcd for C$_{14}$H$_{17}$FN$_2$O$_4$, 296.1172; found, 296.1180. [α]^{20}$_D$ −54° (*c* 0.990, CHCl$_3$). Anal. (C$_{14}$H$_{17}$-FN$_2$O$_4$) C, H, N.

(*R*)-[*N*-3-(3-Fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methyl Methanesulfonate, 6b. To a solution of 30.209 g (101.9 mmol) of **5b** and 28.0 mL (200.9 mmol) of triethylamine in 600 mL of methylene chloride at 0 °C was added 11.0 mL (142.1 mmol) of methanesulfonyl chloride over 15 min. After 20 min, the mixture was filtered, and the white solid was washed with water (3 × 100 mL) and dried in a vacuum oven to give 27.113 g of **6b** as a white solid. The layers of the filtrate were separated, and the aqueous portion was extracted with methylene chloride (3 × 100 mL). The combined organic portions were dried (MgSO$_4$) and evaporated to give a tan solid (14.055 g). Each lot was recrystallized from acetonitrile and water to give a total of 35.423 g of **6b** as an off-white solid, still contaminated with a mesyl impurity. The mesylate was used "as is" in the next reaction. ^{1}H NMR (DMF, 300 MHz): δ 7.61 (dd, J = 15.0 Hz, J = 2.4 Hz, 1H), 7.27 (dd, J = 8.7 Hz, J = 2.1 Hz, 1H), 7.11 (t, J = 9.3 Hz, 1H), 5.14 (m, 1H), 4.65 (m, 2H), 4.32 (t, J = 9.3 Hz, 1H), 3.99 (dd, J = 9.3 Hz, J = 6.3 Hz, 1H), 3.78 (t, J = 4.5 Hz, 4H), 3.34 (s, 3H), 3.02 (t, J = 4.5 Hz, 4H). IR (mineral oil mull, cm^{-1}): 2925, 1752, 1516, 1356, 1347, 1231, 1183, 1112. MS: *m/z* 374 (100, M$^+$), 316 (43.1), 176 (11.9), 150 (12.5), 149 (15.5). Exact mass: calcd for C$_{15}$H$_{19}$FN$_2$O$_6$S, 374.0948; found, 374.0952. [α]^{20}$_D$ −50° (*c* 0.998, DMF).

(*R*)-[*N*-3-(3-Fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methyl Azide, 8b. A mixture of 20.55 g (53.06 mmol) of **6b** and 13.230 g (203.47 mmol) of sodium azide in 400 mL of dimethylformamide was heated at 75 °C for 16 h, at which time, after cooling, water (750 mL) and ethyl acetate (300 mL) were added. The phases were separated, and the aqueous portion was extracted with ethyl acetate (3 × 200 mL). The combined organic portions were dried (MgSO$_4$) and evaporated to give 18.037 g of **8b**, which was not purified. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.44 (dd, J = 14.4 Hz, J = 2.7 Hz, 1H), 7.13 (dd, J = 8.7 Hz, J = 2.7 Hz, 1H), 6.94 (t, J = 9.0 Hz, 1H), 4.78 (m, 1H), 4.05 (t, J = 9.0 Hz, 1H), 3.87 (t, J = 4.5 Hz, 4H), 3.83 (dd, J = 9.0 Hz, J = 6.3 Hz, 1H), 3.70 (dd, J = 13.2 Hz, J = 4.5 Hz, 1H), 3.59 (dd, J = 13.2 Hz, J = 4.5 Hz, 1H), 3.05 (t, J = 4.5 Hz, 4H). IR (mineral oil mull, cm^{-1}): 2096, 1746, 1519, 1478, 1448, 1416, 1225, 1112. MS: *m/z* 321 (100, M$^+$), 191 (80.5), 190 (56.6), 164 (27.8), 150 (54.5), 149 (24.3), 81 (19.3), 42 (18.2). Exact mass: calcd for C$_{14}$H$_{16}$FN$_5$O$_3$, 321.1237; found, 321.1245.

(*S*)-*N*-[[3-(3-Fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide, U-100766. To a solution of 16.711 g (49.16 mmol) of azide **8b** in 300 mL of ethyl acetate was added 0.220 g of 10% palladium on carbon, and the system was alternately evacuated and filled with nitrogen; then hydrogen was introduced *via* a balloon system, with three cycles of evacuation and filling from the balloon. The mixture was stirred overnight, and then additional 0.238 g of palladium black and hydrogen were added; after 6 h, 0.535 g of 10% palladium on carbon was added with more hydrogen and left to stir overnight. The reaction mixture was then evacuated and flushed with nitrogen and cooled to 0 °C, and 4.6 mL (56.87 mmol) of pyridine and 15.0 mL (159.0 mmol) of acetic anhydride were added. The mixture was stirred for 30 min and then removed from the ice bath and stirred at room temperature for 1 h; then it was filtered through a plug of diatomaceous earth and concentrated to give 26.112 g of crude U-100766 as an orange solid. This was purified on a medium pressure silica gel column (5.5 cm × 34 cm, eluted with concentration gradient of 3−10% methanol−ethyl acetate), to give upgraded material. This was again submitted to chromatography and then recrystallized from ethyl acetate and hexanes to give 11.244 g (68.8% yield from **5b**) of U-100766

as white crystals, mp 181.5−182.5 °C. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.43 (dd, J = 14.4 Hz, J = 2.8 Hz, 1H), 7.07 (dd, J = 8.8 Hz, J = 2.0 Hz, 1H), 6.92 (t, J = 9.2 Hz, 1H), 6.19 (br t, 1H), 4.77 (m, 1H), 4.02 (t, J = 8.8 Hz, 1H), 3.87 (t, J = 4.8 Hz, 4H), 3.76 (dd, J = 9.2 Hz, J = 6.8 Hz, 1H), 3.69 (ddd, J = 11.6 Hz, J = 6.0 Hz, J' = 3.2 Hz, 1H), 3.63 (dt, J = 14.8 Hz, J = 6.0 Hz, 1H), 3.05 (t, J = 4.8 Hz, 4H), 2.02 (s, 3H). ^{13}C NMR (100.62 MHz, CDCl$_3$): 23.34, 42.23, 48.00, 51.32 (d, J = 3.02 Hz), 67.28, 72.43, 107.90 (d, J = 26.36 Hz), 114.35 (d, J = 3.32 Hz), 119.19 (d, J = 4.12 Hz), 133.28 (d, J = 10.26 Hz), 136.88 (d, J = 9.05 Hz), 154.90, 155.79 (d, J = 246.22 Hz), 171.75. IR (mineral oil mull, cm^{-1}): 3284, 3092, 1753, 1728, 1649, 1565, 1519, 1447, 1435. MS: *m/z* 337 (100, M$^+$), 293 (35.8), 234 (35.3), 209 (47.2), 176 (28.4), 164 (24.6), 151 (27.8), 150 (23.1), 138 (22.0), 43 (26.1). Exact mass: calcd for C$_{16}$H$_{20}$-FN$_3$O$_4$, 337.1438; found, 337.1444. = [α]^{20}$_D$ −9° (*c* 0.919, CHCl$_3$). Anal. (C$_{16}$H$_{20}$FN$_3$O$_4$) C, H, N.

***In Vitro* Tests.** MICs for aerobic Gram-positive bacteria were determined by agar dilution or broth microdilution methodology, corresponding to the National Committee for Clinical Laboratory Standards.[43] In the MIC determinations for *M. tuberculosis*, the compounds were incorporated into 7H10 agar medium (Difco Laboratories, Detroit, MI) at concentrations of 2.0, 0.50, 0.125, and 0.03 mg/mL. The *M. tuberculosis* test organism was grown in 7H9 medium (Difco) containing 0.05% Tween 80. After 7 days of incubation at 37 °C, the broths were adjusted to the turbidity of a 1.0 McFarland standard; the organisms were then diluted 10-fold in sterile water containing 0.10% Tween 80. The resultant bacterial suspensions were spotted onto the drug-supplemented 7H10 plates. After a 21 day cultivation at 37 °C, the growth of the organisms was scored. The MIC was defined as the lowest concentration of drug that completely inhibited growth of the organism.

***In Vivo* Tests.** ED$_{50}$ evaluations were carried out in CF1 female mice (Harlan Sprague−Dawley, Indianapolis, IN) injected intraperitoneally with sufficient bacteria to kill 100% of the untreated animals for all methicillin-sensitive and methicillin-resistant *S. aureus* strains. C3H/HeN female mice (Charles River Laboratories, Raleigh, NC) were utilized in the tests for *E. faecalis* UC12379 and *E. faecium* UC15090. Thawed bacterial cultures were suspended in BHI broth which contained 4−8% dried Brewer's yeast (w/v) (Champlain Industries Inc., Clifton, NJ). The infecting inoculum (0.2 mL) was adjusted to yield *ca.* 100 times the 50% lethal dose (LD$_{50}$). Concurrently with each trial, the challenge LD$_{50}$ was validated by inoculating untreated animals with log dilutions of the bacteria. Five dosage levels representing a 5 log dilution range were employed per determination with 10 mice utilized at each level. A mortality rate of 90−100% was produced in all groups of untreated mice with the 100× LD$_{50}$ challenge inoculum. Oxazolidinones were formulated in water or saline, with gentle heating at higher concentrations, and administered orally or subcutaneously at 1 and 5 h postinfection. At least five dosage levels of antibiotic utilizing serial 2-fold dilutions were employed for each ED$_{50}$ determination. One treatment group of six mice was used for each antibiotic dosage level. Deaths in each group following infection and treatment were monitored daily for at least 6 days. Following this observation period, cumulative mortality figures were used to calculate by probit analysis the amount of drug in mg of drug/kg of body weight/dose required to protect 50% of the lethally infected mice. For experiments using the *E. faecium* model, C3H/HeN mice were rendered neutropenic by two intraperitoneal injections of 200 mg/kg cyclophosphamide (Sigma Chemical Co.) separated by an interval of 40 h. Mice were infected intraperitoneally with *E. faecium* 14 h following the last cyclophosphamide dose. In the neutropenic mouse model, antibiotic was administered 1 and 5 h postinfection and twice a day thereafter for 4 days.

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